Novel use of imidazotriazinones

The present invention relates to the use of known imidazotriazinones for producing a medicament for the treatment and/or prophylaxis of coronary heart disease, heart failure, pulmonary hypertension, bladder disorders, prostate hyperplasia, nitrate-induced tolerance, ocular disorders such as glaucoma, for the treatment or prophylaxis of central retinal or posterior cilliary arterial occlusion, central retinal venous occlusion, optic neuropathy such as anterior ischemic optic neuropathy and glaucomatous optic neuropathy, and of macular degeneration, diabetes, especially of diabetic gastroparesis, for the treatment of disorders of the peristalsis of stomach and esophagus, female infertility, premature labor, preeclampsia, alopecia, psoriasis, the renal syndrome, cystic fibrosis, cancer, for improving perception, for improving concentration, for improving learning and/or memory, especially if the impairment is a consequence of dementia.

Imidazotriazinones are described in WO-A 01/64677, the compounds disclosed therein being suitable for the treatment of erectile dysfunction.

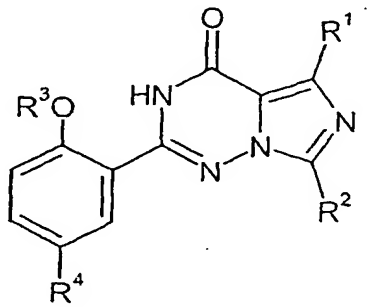
German published specification 2811780 describes imidazotriazines as bronchodilators with spasmolytic activity and inhibitory activity on phosphodiesterases which metabolize cyclic adenosine monophosphate (cAMP PDEs, also referred to as PDE III and PDE IV according to the Beavo nomenclature). An inhibitory effect on phosphodiesterases which metabolise cyclic guanosine monophosphate [cGMP PDEs, also referred to as PDE I, PDE II and PDE V according to the nomenclature of Beavo and Reifsnyder (Trends in Pharmacol. Sci. 11, 150-155, 1990)] is not described. In addition, imidazotriazinones which have no substituted aryl radical in the 2 position are described in FR 22 13 058, CH 59 46 71, DE 22 55 172, DE 23 64 076 and EP 000 9384, and are likewise described as bronchodilators with cAMP PDE-inhibitory effect.

WO-A 99/24433 likewise describes imidazotriazinones as cGMP-metabolizing phosphodiesterase inhibitors, but it is obligatory for them to have a sulfonamide group in the position para to the alkoxy group in the phenyl ring.

An increase in the cGMP concentration may lead to therapeutic, antiaggregatory, antithrombotic, antiproliferative, antivasospastic, vasodilating, natriuretic and diuretic effects. It may influence the short- or long-term modulation of vascular and cardiac inotropy, the heart rhythm and cardiac conduction (J.C. Stoclet, T. Keravis, N. Komas and C. Kugnier, Exp. Opin. Invest. Drugs (1995), 4 (11), 1081-1100).

The relaxant effect on smooth muscle leads to a therapeutic improvement in the microcirculation in tissues which comprise cGMP-metabolizing phosphodiesterases.

It has now been found that compounds of the general formula (I)



(I),

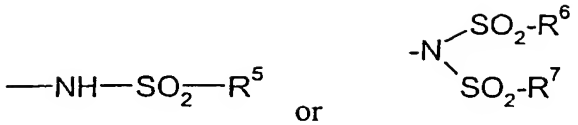
in which

R^1 is (C_1-C_6)-alkyl,

R^2 is (C_3-C_8)-cycloalkyl or (C_1-C_{12})-alkyl,

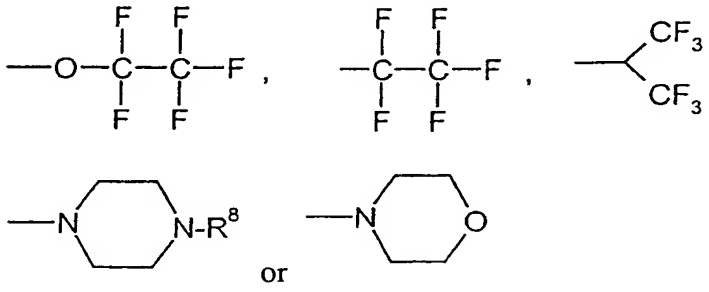
R^3 is (C_1-C_6)-alkyl,

R^4 is a radical of the formulae



in which

R^5, R^6 and R^7 are identical or different and are vinyl or (C_1-C_6)-alkyl which is optionally substituted up to 3 times, identically or differently, by trifluoromethyl, halogen, (C_1-C_6)-alkoxy or by radicals of the formulae



in which

R^8 is hydrogen or (C_1-C_4)-alkyl,

or

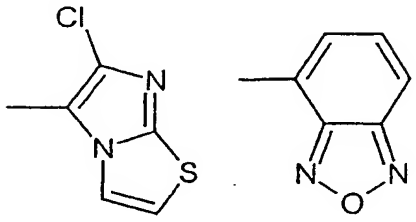
R^5, R^6 and/or R^7 are (C_6-C_{12})-aryl which is optionally substituted up to 3 times, identically or differently, by halogen, trifluoromethyl, nitro, cyano, carboxyl, (C_1-C_6)-alkyl or (C_1-C_6)-alkoxy,

or

R^5 is quinolyl or a 5- to 6-membered, aromatic or saturated heterocycle having up to 3 heteroatoms from the series S, N and/or O, which may optionally be substituted, in the case of an N function also via the latter, up to 3 times, identically or differently, by halogen or (C_1-C_6)-alkyl,

or

R^5 is a radical of the formulae



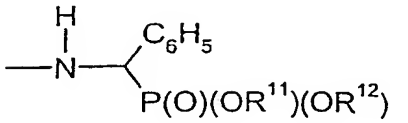
, or $-NR^9R^{10}$,

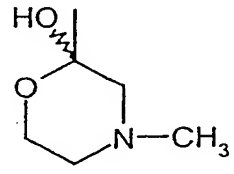
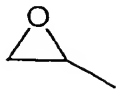
in which

R^9 and R^{10} are identical or different and are hydrogen, (C_1-C_6)-alkyl or phenyl,

or

R^4 is carboxyl or is a radical of the formulae



,  ,  ,

$-CO-R^{13}$ or $-O-R^{14}$,

in which

R^{11} and R^{12} are identical or different and are hydrogen or (C_1-C_4)-alkyl,

R^{13} is (C_1-C_6)-alkyl,

R^{14} is $(C_1\text{-}C_6)$-alkyl which is optionally substituted up to 3 times, identically or differently, by hydroxyl, phenyl or by a radical of the formula $-NR^{15}R^{16}$,

in which

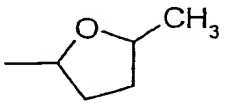
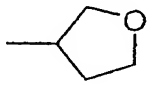
R^{15} and R^{16} are identical or different and are hydrogen, phenyl or $(C_1\text{-}C_4)$-alkyl which in turn may be substituted by phenyl,

or

R^4 is a radical of the formula $-NH\text{-}CO\text{-}NR^{17}R^{18}$,

in which

R^{17} and R^{18} are identical or different and are hydrogen or $(C_1\text{-}C_6)$-alkyl which is optionally substituted by hydroxyl or by a radical of the formulae

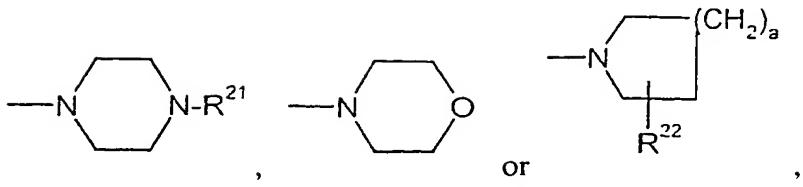

,  or $-NR^{19}R^{20}$,

in which

R^{19} and R^{20} are identical or different and are hydrogen, phenyl or $(C_1\text{-}C_6)$-alkyl,

or

R^{17} and R^{18} form together with the nitrogen atom to which they are bonded a heterocyclic ring of the formulae



in which

R^{21} is hydrogen or $(C_1\text{-}C_6)$-alkyl,

a is either 1 or 2,

R^{22} is hydroxyl or $(C_1\text{-}C_6)$-alkyl which is optionally substituted by hydroxyl,

or

R^{17} and/or R^{18} are $(C_6\text{-}C_{12})$-aryl which is optionally substituted by halogen, trifluoroethyl or by $-SCF_3$,

or

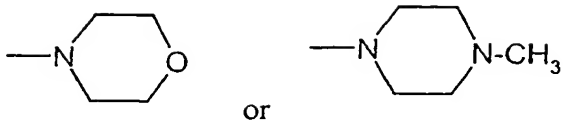
R^{17} is hydrogen and

R^{18} is a radical of the formula $-SO_2\text{-}R^{23}$,

in which

R^{23} is $(C_1\text{-}C_6)$-alkyl or $(C_6\text{-}C_{12})$-aryl which is optionally substituted by halogen,

or is a radical of the formulae



or

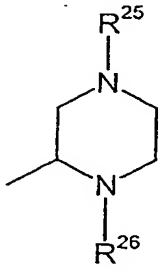
or

R^4 is a radical of the formula

$-NH-CO-R^{24}$,

in which

R^{24} is a radical of the formula



in which

R^{25} and R^{26} are identical or different and are hydrogen, (C_1-C_6)-alkyl or (C_1-C_6)-alkoxycarbonyl,

or

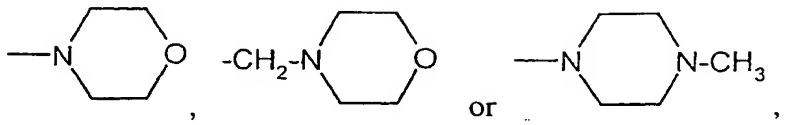
R^{24} is (C_1-C_6)-alkyl which is optionally substituted by (C_6-C_{12})-aryl which in turn may be substituted by hydroxyl or (C_1-C_6)-alkoxy or

(C_1-C_6)-alkyl is optionally substituted by a radical of the formula $-(SO_2)_b-R^{27}$,

in which

b is either 0 or 1, and

R^{27} is a radical of the formulae



or

or

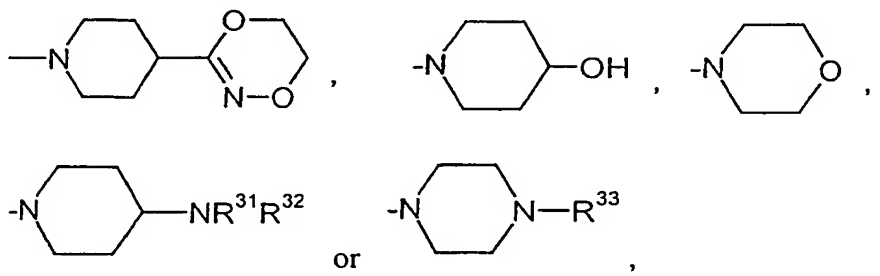
R^4 is $(C_1\text{-}C_{12})$-alkyl which is optionally substituted up to 3 times, identically or differently, by hydroxyl, azide, phenyl or by radicals of the formulae $-NR^{28}R^{29}$, $-O\text{-}CO\text{-}R^{30}$ or $-P(O)\{O\text{-}[(C_1\text{-}C_6)\text{-alkyl}]\}_2$,

in which

R^{28} and R^{29} are identical or different, are hydrogen, phenyl or $(C_1\text{-}C_6)$-alkyl which is optionally substituted by hydroxyl, $(C_1\text{-}C_6)$-alkoxy or phenyl,

or

R^{28} and R^{29} form together with the nitrogen atom to which they are bonded a heterocyclic ring of the formulae



or

in which

R^{31} and R^{32} are identical or different and are hydrogen or (C_1-C_6)-alkyl,

R^{33} is (C_1-C_6)-alkyl, benzyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkylcarbonyl, carboxyl, pyridyl, pyrimidyl or phenyl which is optionally substituted by (C_1-C_6)-alkoxy,

and

R^{30} is (C_1-C_6)-alkyl,

or

(C_1-C_{12})-alkyl is optionally substituted by triazolyl which may in turn be substituted up to twice, identically or differently, by halogen, phenyl, tetrahydrofuranyl, tetrahydropyranyl, (C_1-C_6)-alkoxycarbonyl, aminocarbonyl or by (C_1-C_6)-alkyl, where the latter can optionally be substituted by hydroxyl, (C_1-C_6)-alkoxy or by a radical of the formulae $NR^{34}R^{35}$ or $-O-CO-R^{36}$,

in which

R^{34} and R^{35} are identical or different and are hydrogen or (C_1-C_6)-alkyl,

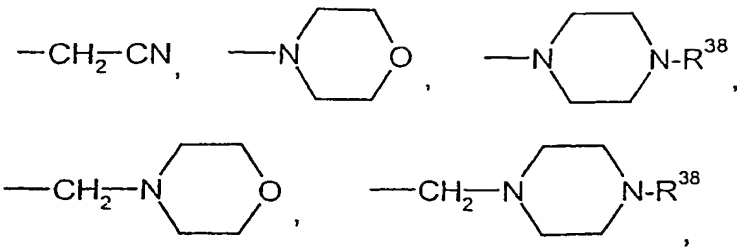
R^{36} is (C_1-C_6)-alkyl,

or

R^4 is a radical of the formula $-CO-R^{37}$,

in which

R^{37} is a radical of the formulae



$-(CH_2)_c-NR^{39}R^{40}$ or $-CH_2-P(O)(OR^{41})(OR^{42})$,

in which

R^{38} is hydrogen or (C_1-C_6)-alkyl,

c is either 0 or 1,

R^{39} and R^{40} are identical or different and are hydrogen or (C_1-C_6)-alkyl, which is optionally substituted by hydroxyl,

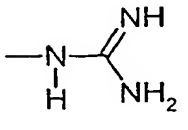
R^{41} and R^{42} are identical or different and are (C_1-C_6)-alkyl,

or

R^4 is a 5-membered heterocycle having up to 3 heteroatoms from the series S, N and/or O which is optionally substituted, in the case of an N function also via the latter, a total of up to 3 times, identically or differently, by halogen, trifluoromethyl or by phenyl which may in turn be substituted one or more times by halogen or trifluoromethyl,

and/or is optionally substituted by (C_3-C_6)-cycloalkyl, pyrryl or (C_1-C_{12})-alkyl which may in turn be substituted by cyano, trifluoromethyl, (C_1-C_6)-

alkoxycarbonyl, (C_1-C_6)-alkoxy, amino or by phenyl or nitro-substituted phenyl,

and/or may optionally be substituted by $-NR^{43}R^{44}$, -NH-CO-CO-R^{45}, -NH-CO-R^{46}, -NH-CO-CH_2-R^{47}, -CO-R^{48} or  ,

in which

R^{43} and R^{44} are identical or different and are hydrogen, benzyl (C_1-C_6)-alkyl or phenyl which is optionally substituted by halogen or trifluoromethyl,

R^{45} is (C_1-C_6)-alkoxy,

R^{46} is (C_1-C_6)-alkyl or phenyl,

R^{47} is hydroxyl, (C_1-C_6)-alkoxy or a radical of the formula $-O-CO-R^{49}$,

in which

R^{49} is (C_1-C_4)-alkyl,

R^{48} is a radical of the formula $-CH_2-CN$ or phenyl which is optionally substituted by halogen, trifluoromethyl or (C_1-C_6)-alkoxy,

and the salts, tautomers, N-oxides, prodrugs and hydrates thereof, and isomeric forms,

are also suitable for producing medicaments which are employed for the treatment of and/or prophylaxis of coronary heart disease, heart failure, pulmonary hypertension, bladder disorders, prostate hyperplasia, nitrate-induced tolerance, ocular disorders

such as glaucoma, for the treatment or prophylaxis of central retinal or posterior cilliary arterial occlusion, central retinal venous occlusion, optic neuropathy such as anterior ischemic optic neuropathy and glaucomatous optic neuropathy, and of macular degeneration, diabetes, especially of diabetic gastroparesis, for the treatment of disorders of the peristalsis of stomach and esophagus, female infertility, premature labor, preeclampsia, alopecia, psoriasis, the renal syndrome, cystic fibrosis, cancer, for improving perception, for improving concentration, for improving learning and/or memory, in particular if the impairment is a consequence of dementia.

The compounds of the general formula (I) may, depending on the substitution pattern, exist in stereoisomeric forms which either are related as image and mirror image (enantiomers) or which are not related as image and mirror image (diastereomers). The invention relates both to the enantiomers or diastereomers and to respective mixtures thereof. The racemic forms can, just like the diastereomers, be separated into the stereoisomerically pure constituents in a known manner.

Certain compounds of the general formula (I) may moreover exist in tautomeric forms. This is known to the skilled worker, and such compounds are likewise included within the scope of the invention.

Physiologically acceptable, i.e. pharmaceutically suitable salts may be salts of the compounds of the invention with inorganic or organic acids. Preferred salts are those with inorganic acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid or sulfuric acid, or salts with organic carboxylic or sulfonic acids such as, for example, acetic acid, propionic acid, maleic acid, fumaric acid, malic acid, citric acid, tartaric acid, lactic acid, benzoic acid, or methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid or naphthalenedisulfonic acid.

Pharmaceutically acceptable salts which may also be mentioned are salts with conventional bases such as, for example, alkali metal salts (e.g. sodium or potassium salts), alkaline earth metal salts (e.g. calcium or magnesium salts) or ammonium salts derived from ammonia or organic amines such as, for example, diethylamine,

triethylamine, ethyldiisopropylamine, procaine, dibenzylamine, N-methylmorpholine, dihydroabietylamine or methylpiperidine.

"Hydrates" refer according to the invention to those forms of the compounds of the above general formula (I) which form a molecular compound (solvate) in the solid or liquid state by hydration with water. The water molecules in the hydrates are attached through secondary valences by intramolecular forces, in particular hydrogen bonds. Solid hydrates contain water as so-called water of crystallization in stoichiometric ratios, and the water molecules do not have to be equivalent in terms of their binding state. Examples of hydrates are sesquihydrates, monohydrates, dihydrates or trihydrates. Equally suitable are also the hydrates of salts of the compounds of the invention.

"Prodrugs" refer according to the invention to those forms of the compounds of the above general formula (I) which may themselves be biologically active or inactive but can be converted into the corresponding biologically active form (for example metabolically, solvolytically or in another way).

$(C_1\text{-}C_{12})$-Alkyl is a straight-chain or branched alkyl radical having 1 to 12 carbon atoms. Examples which may be mentioned are: methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl and n-hexyl. The corresponding alkyl groups with fewer carbon atoms are derived analogously from this definition, such as, for example, $(C_1\text{-}C_6)$-alkyl and $(C_1\text{-}C_4)$-alkyl. It is generally true that $(C_1\text{-}C_4)$-alkyl is preferred.

$(C_3\text{-}C_8)$-Cycloalkyl is a cyclic alkyl radical having 3 to 8 carbon atoms. Examples which may be mentioned are: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl. The corresponding cycloalkyl groups with fewer carbon atoms are derived analogously from this definition, such as, for example, $(C_3\text{-}C_5)$-cycloalkyl. Cyclopropyl, cyclopentyl and cyclohexyl are preferred.

$(C_1\text{-}C_6)$-Alkoxy is a straight-chain or branched alkoxy radical having 1 to 6 carbon atoms. Examples which may be mentioned are: methoxy, ethoxy, n-propoxy,

isopropoxy, n-butoxy, isobutoxy, tert-butoxy, n-pentoxy and n-hexoxy. The corresponding alkoxy groups with fewer carbon atoms are derived analogously from this definition, such as, for example, (C_1-C_6)-alkoxy and (C_1-C_4)-alkoxy. It is generally true that (C_1-C_4)-alkoxy is preferred.

Also derived from this definition is the meaning of the corresponding component of another more complex substituent such as, for example, alkoxycarbonyl.

(C_6-C_{12})-Aryl is an aromatic radical having 6 to 12 carbon atoms. Examples which may be mentioned are: phenyl and naphthyl.

5- to 6-membered, aromatic or saturated heterocycle having up to 3 heteroatoms from the series S, N and/or O is either a heteroaromatic system which is linked via a ring carbon atom of the heteroaromatic system, where appropriate also via a ring nitrogen atom of the heteroaromatic system; examples which may be mentioned are: pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, thienyl, furyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl or isoxazolyl, with preference for pyridyl, pyrimidyl, pyridazinyl, furyl and thienyl, or is a saturated heterocycle which is linked via a ring carbon atom or a ring nitrogen atom, or is a (C_5-C_6)-cycloalkyl radical as defined above; examples which may be mentioned are: tetrahydrofuryl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, cyclopentyl and cyclohexyl, with preference for piperdinyl, morpholinyl and pyrrolidinyl.

It is preferred to use according to the invention compounds of the general formula (I)

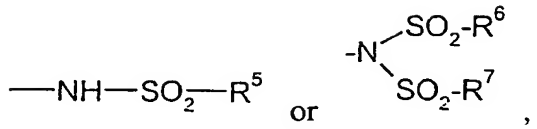
in which

R^1 is (C_1-C_4)-alkyl,

R^2 is cyclopentyl, cycloheptyl or (C_1-C_{10})-alkyl,

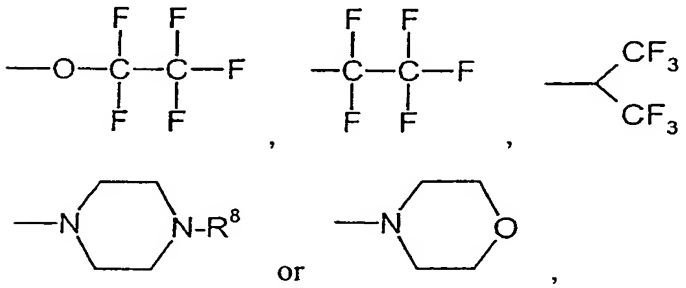
R^3 is (C_1-C_4)-alkyl,

R^4 is a radical of the formulae



in which

R^5, R^6 and R^7 are identical or different and are vinyl or (C_1-C_4)-alkyl which is optionally substituted up to 3 times, identically or differently, by trifluoromethyl, chlorine, (C_1-C_4)-alkoxy or by radicals of the formulae



in which

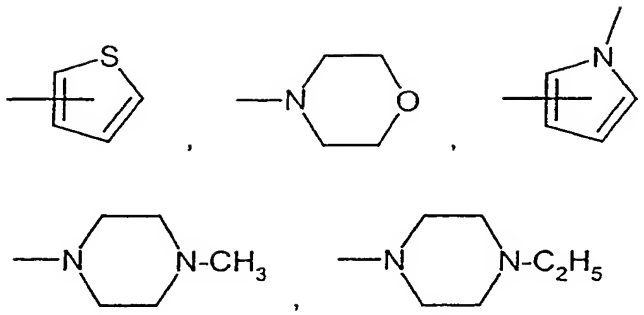
R^8 is hydrogen, methyl or ethyl,

or

R^5, R^6 and/or R^7 are phenyl which is optionally substituted up to 3 times, identically or differently by halogen, trifluoromethyl, nitro, cyano, carboxyl, (C_1-C_4)-alkyl or (C_1-C_4)-alkoxy,

or

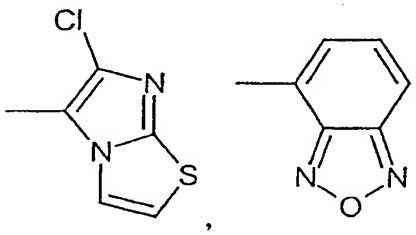
R^5 is quinolyl or a radical of the formulae



which may optionally be substituted up to twice, identically or differently, by chlorine or (C_1-C_4)-alkyl,

or

R^5 is a radical of the formulae



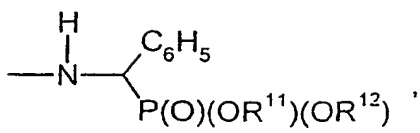
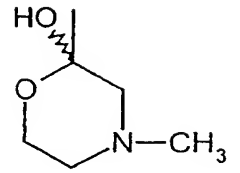
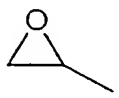
or $-NR^9R^{10}$,

in which

R^9 and R^{10} are identical or different and are hydrogen, (C_1-C_6)-alkyl or phenyl,

or

R^4 is carboxyl or is a radical of the formulae

-CO-R^{13} or –O-R^{14},

in which

R^{11} and R^{12} are identical or different and are hydrogen or (C_1-C_4)-alkyl,

R^{13} is (C_1-C_4)-alkyl,

R^{14} is (C_1-C_4)-alkyl which is optionally substituted up to 3 times, identically or differently, by hydroxyl, phenyl or by a radical of the formula –$NR^{15}R^{16}$,

in which

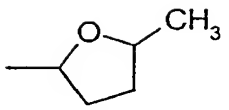
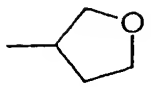
R^{15} and R^{16} are identical or different and are hydrogen, phenyl or (C_1-C_4)-alkyl which may in turn be substituted by phenyl,

or

R^4 is a radical of the formula –NH-CO-$NR^{17}R^{18}$,

in which

R^{17} and R^{18} are identical or different and are hydrogen or (C_1-C_4)-alkyl which is optionally substituted by hydroxyl or by a radical of the formulae

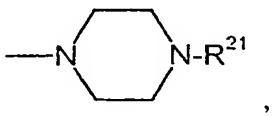
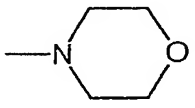
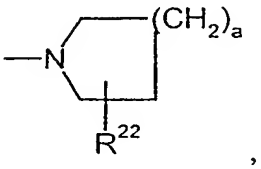

,  or $-NR^{19}R^{20}$,

in which

R^{19} and R^{20} are identical or different and are hydrogen, phenyl or (C_1-C_4)-alkyl,

or

R^{17} and R^{18} form together with the nitrogen atom to which they are bonded a heterocyclic ring of the formulae


,  or 
,

in which

R^{21} is hydrogen or (C_1-C_4)-alkyl,

a is either 1 or 2,

R^{22} is hydroxyl or (C_1-C_4)-alkyl which is optionally substituted by hydroxyl,

or

R^{17} and/or R^{18} are phenyl which is optionally substituted by chlorine, trifluoroethyl or by $-SCF_3$,

or

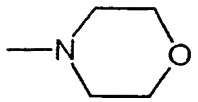
R^{17} is hydrogen, and

R^{18} is a radical of the formula $-SO_2-R^{23}$,

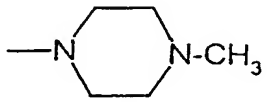
in which

R^{23} is (C_1-C_4)-alkyl or phenyl which is optionally substituted by halogen,

or is a radical of the formulae



or



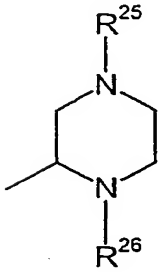
or

R^4 is a radical of the formula

$-NH-CO-R^{24}$

in which

R^{24} is a radical of the formula



in which

R^{25} and R^{26} are identical or different and are hydrogen, (C_1-C_4)-alkyl or (C_1-C_4)-alkoxycarbonyl,

or

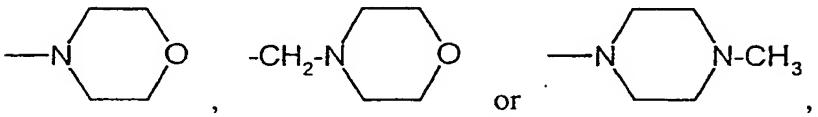
R^{24} is (C_1-C_4)-alkyl which is optionally substituted by phenyl which may in turn be substituted by hydroxyl or (C_1-C_4)-alkoxy, or

(C_1-C_4)-alkyl is optionally substituted by a radical of the formula $-(SO_2)_b-R^{27}$

in which

b is either 0 or 1, and

R^{27} is a radical of the formulae



or

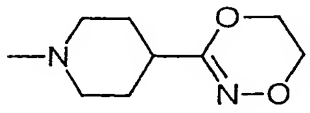
R^4 is (C_1-C_{11})-alkyl which is optionally substituted up to 3 times, identically or differently, by hydroxyl, azide, phenyl or by radicals of the formulae $-NR^{28}R^{29}$, $-O-CO-R^{30}$ or $-P(O)\{O-[(C_1-C_6)\text{-alkyl}]\}_2$,

in which

R^{28} and R^{29} are identical or different and are hydrogen, phenyl or (C_1-C_4)-alkyl which is optionally substituted by hydroxyl, (C_1-C_4)-alkoxy or phenyl,

or

R^{28} and R^{29} form together with the nitrogen atom to which they are bonded a heterocyclic ring of the formulae



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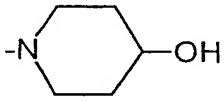

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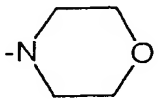

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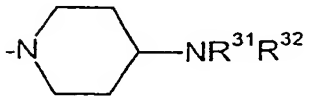
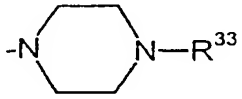


or


,

in which

R^{31} and R^{32} are identical or different and are hydrogen or (C_1-C_4)-alkyl,

R^{33} is (C_1-C_4)-alkyl, benzyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylcarbonyl, carboxyl, pyridyl, pyrimidyl or phenyl which is optionally substituted by (C_1-C_4)-alkoxy,

and

R^{30} is (C_1-C_6)-alkyl,

or

$(C_1$-$C_{11})$-alkyl is optionally substituted by triazolyl which may in turn be substituted up to twice, identically or differently, by halogen, phenyl, tetrahydrofuranyl, tetrahydropyranyl, $(C_1$-$C_4)$-alkoxycarbonyl, aminocarbonyl or by $(C_1$-$C_4)$-alkyl, where the latter may optionally be substituted by hydroxyl, $(C_1$-$C_4)$-alkoxy or by a radical of the formulae $NR^{34}R^{35}$ or $-O-CO-R^{36}$,

in which

R^{34} and R^{35} are identical or different and are hydrogen or $(C_1$-$C_4)$-alkyl,

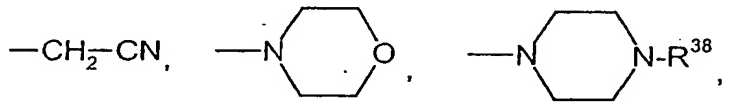
R^{36} is $(C_1$-$C_4)$-alkyl,

or

R^4 is a radical of the formula $-CO-R^{37}$

in which

R^{37} is a radical of the formulae



$-(CH_2)_c-NR^{39}R^{40}$ or $-CH_2-P(O)(OR^{41})(OR^{42})$,

in which

R^{38} is hydrogen or (C_1-C_4)-alkyl,

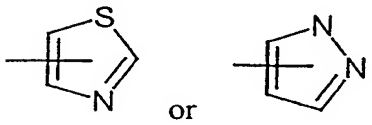
c is either 0 or 1,

R^{39} and R^{40} are identical or different and are hydrogen or (C_1-C_4)-alkyl which is optionally substituted by hydroxyl,

R^{41} and R^{42} are identical or different and are (C_1-C_4)-alkyl,

or

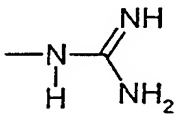
R^4 is a radical of the formula



which is optionally substituted, in the case of pyrazole also via the N function, a total of up to 3 times, identically or differently, by chlorine, trifluoromethyl or by phenyl which may in turn be substituted one or more times by chlorine or trifluoromethyl,

and/or is optionally substituted by cyclopentyl, cyclohexyl, pyrryl or (C_1-C_{12})-alkyl which may in turn be substituted by cyano, trifluoromethyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkoxy, amino or by phenyl or nitro-substituted phenyl,

and/or may also be substituted by $-NR^{43}R^{44}$, -NH-CO-CO-R^{45}, -NH-CO-R^{46},

-NH-CO-CH_2-R^{47}, -CO-R^{48} or  ,

in which

R^{43} and R^{44} are identical or different and are hydrogen, benzyl, (C_1-C_4)-alkyl or phenyl which is optionally substituted by halogen or trifluoromethyl,

R^{45} is (C_1-C_5)-alkoxy,

R^{46} is (C_1-C_5)-alkyl or phenyl,

R^{47} is hydroxyl, (C_1-C_4)-alkoxy or a radical of the formula $-O-CO-R^{49}$,

in which

R^{49} is (C_1-C_3)-alkyl,

R^{48} is a radical of the formula $-CH_2-CN$ or phenyl which is optionally substituted by chlorine, trifluoromethyl or (C_1-C_4)-alkoxy,

and the N-oxides and/or tautomers thereof, and the pharmaceutically suitable salts, hydrates and prodrugs thereof.

Particular preference is given to the compounds of the invention of the general formula (I)

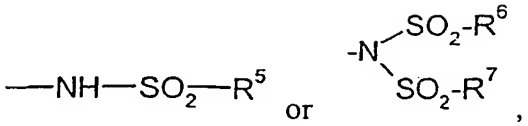
in which

R^1 is (C_1-C_4)-alkyl,

R^2 is cyclopentyl, cyclohexyl, cycloheptyl or (C_1-C_{10})-alkyl,

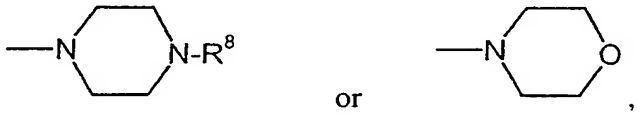
R^3 is (C_1-C_4)-alkyl,

R^4 is a radical of the formulae



in which

R^5, R^6 and R^7 are identical or different and are vinyl or $(C_1$-$C_4)$-alkyl which is optionally substituted up to 3 times, identically or differently, by trifluoromethyl, chlorine, $(C_1$-$C_4)$-alkoxy or by radicals of the formulae



in which

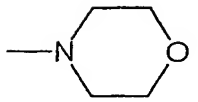
R^8 is hydrogen, methyl or ethyl,

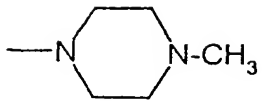
or

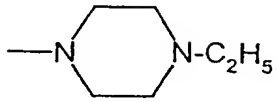
R^5, R^6 and/or R^7 are phenyl which is optionally substituted up to 3 times, identically or differently, by halogen, cyano, $(C_1$-$C_4)$-alkyl or $(C_1$-$C_4)$-alkoxy,

or

R^5 is a radical of the formulae







which may optionally be substituted up to twice, identically or differently, by chlorine or (C_1-C_4)-alkyl,

or

R^5 is a radical of the formula $-NR^9R^{10}$,

in which

R^9 and R^{10} are identical or different and are hydrogen, (C_1-C_4)-alkyl or phenyl,

or

R^4 is carboxyl or is a radical of the formulae

or

$-CO-R^{13}$ or $-O-R^{14}$,

in which

R^{13} is (C_1-C_4)-alkyl,

R^{14} is (C_1-C_4)-alkyl which is optionally substituted up to 3 times, identically or differently, by hydroxyl or by a radical of the formula $-NR^{15}R^{16}$,

in which

R^{15} and R^{16} are identical or different and are hydrogen or (C_1-C_4)-alkyl which in turn may be substituted by phenyl,

or

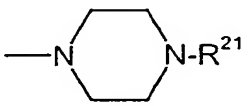
R^4 is a radical of the formula $-NH-CO-NR^{17}R^{18}$,

in which

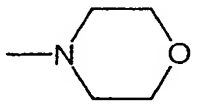
R^{17} and R^{18} are identical or different and are hydrogen or (C_1-C_4)-alkyl which is optionally substituted by hydroxyl,

or

R^{17} and R^{18} form together with the nitrogen atom to which they are bonded a heterocyclic ring of the formulae



or



,

in which

R^{21} is hydrogen or (C_1-C_4)-alkyl,

or

R^{17} and/or R^{18} are phenyl which is optionally substituted by chlorine, trifluoroethyl or by $-SCF_3$,

or

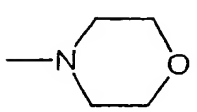
R^{17} is hydrogen, and

R^{18} is a radical of the formula $-SO_2-R^{23}$,

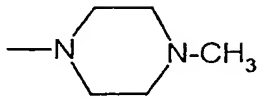
in which

R^{23} is (C_1-C_4)-alkyl or phenyl which is optionally substituted by halogen,

or is a radical of the formulae



or



,

or

R^4 is a radical of the formula

$-NH-CO-R^{24}$,

in which

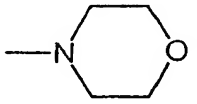
R^{24} is (C_1-C_4)-alkyl which is optionally substituted by phenyl which in turn may optionally be substituted by hydroxyl or (C_1-C_4)-alkoxy, or

(C_1-C_4)-alkyl is optionally substituted by a radical of the formula $-(SO_2)_b-R^{27}$,

in which

b is either 0 or 1, and

R^{27} is a radical of the formulae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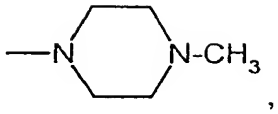

,

or

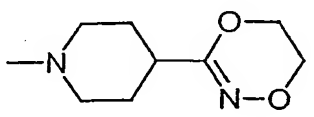
R^4 is (C_1-C_6)-alkyl which is optionally substituted up to 3 times, identically or differently, by hydroxyl, phenyl or by radicals of the formulae $-NR^{28}R^{29}$ or $-O-CO-R^{30}$,

in which

R^{28} and R^{29} are identical or different, are hydrogen, phenyl or (C_1-C_4)-alkyl which is optionally substituted by hydroxyl, (C_1-C_4)-alkoxy or phenyl,

or

R^{28} and R^{29} form together with the nitrogen atom to which they are bonded a heterocyclic ring of the formulae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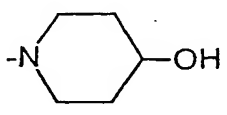
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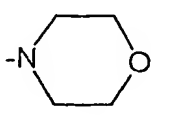
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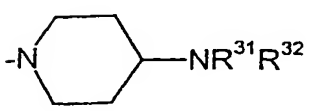
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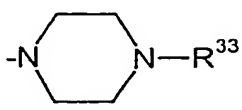


in which

R^{31} and R^{32} are identical or different and are hydrogen or (C_1-C_4)-alkyl,

R^{33} is (C_1-C_4)-alkyl, benzyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylcarbonyl, carboxyl, pyridyl, pyrimidyl or phenyl which is optionally substituted by (C_1-C_4)-alkoxy,

and

R^{30} is (C_1-C_6)-alkyl,

or

(C_1-C_6)-alkyl is optionally substituted by triazolyl which may in turn be substituted up to twice, identically or differently, by (C_1-C_4)-alkyl, where the latter may optionally be substituted by hydroxyl or (C_1-C_4)-alkoxy,

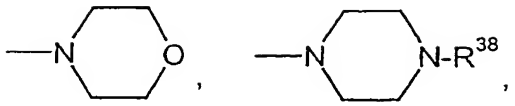
in which

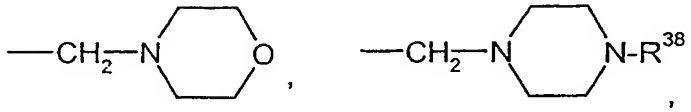
or

R^4 is a radical of the formula $-CO-R^{37}$,

in which

R^{37} is a radical of the formulae





or $-(CH_2)_c-NR^{39}R^{40}$,

in which

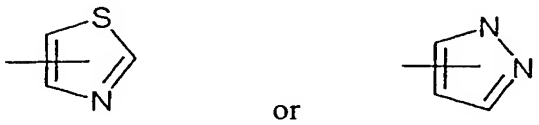
R^{38} is hydrogen or (C_1-C_4)-alkyl,

c is either 0 or 1,

R^{39} and R^{40} are identical or different and are hydrogen or (C_1-C_4)-alkyl which is optionally substituted by hydroxyl,

or

R^4 is a radical of the formula



which is optionally substituted, in the case of pyrazole also via the N function, a total of up to 3 times, identically or differently, by trifluoromethyl or by phenyl which may in turn be substituted one or more times by chlorine or trifluoromethyl,

and/or is optionally substituted by cyclopentyl, cyclohexyl or by (C_1-C_6)-alkyl which may in turn be substituted by (C_1-C_4)-alkoxy, amino or by phenyl,

and/or may optionally be substituted by $-NR^{43}R^{44}$, $-NH-CO-R^{46}$, $-NH-CO-CH_2-R^{47}$ or $-CO-R^{48}$,

in which

R^{43} and R^{44} are identical or different and are hydrogen, benzyl, (C_1-C_4)-alkyl or phenyl which is optionally substituted by halogen or trifluoromethyl,

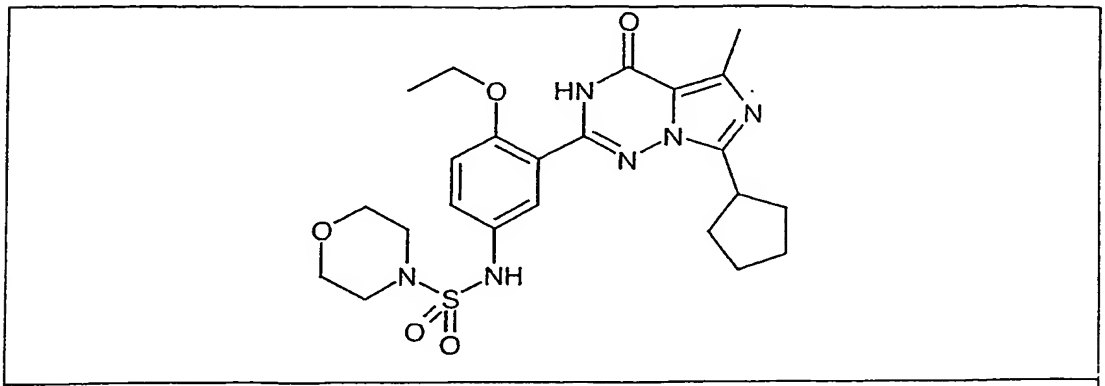
R^{46} is (C_1-C_4)-alkyl or phenyl,

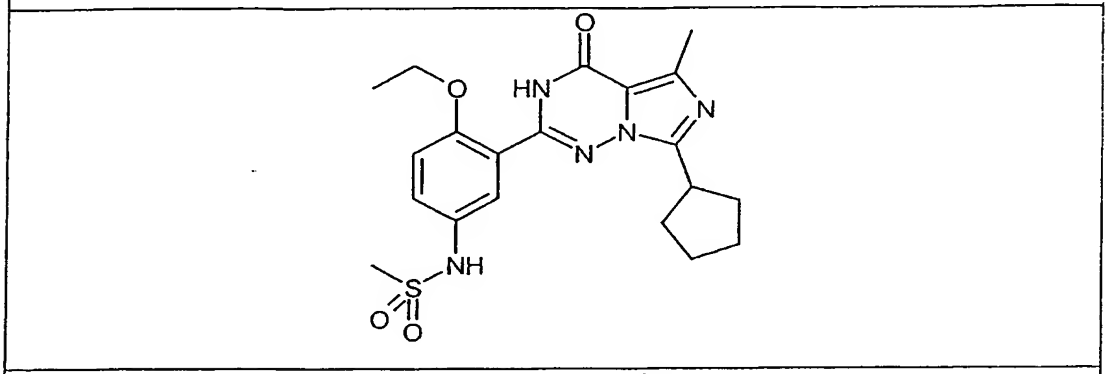
R^{47} is hydroxyl or (C_1-C_4)-alkoxy,

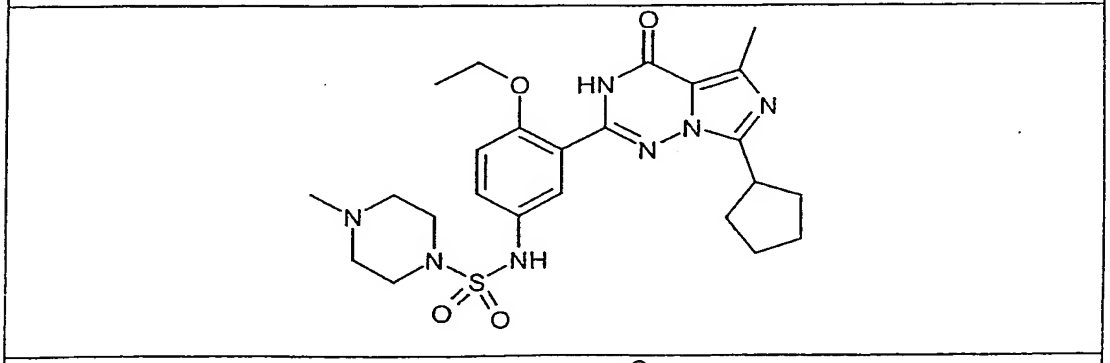
R^{48} is phenyl which is optionally substituted by chlorine, trifluoromethyl or (C_1-C_4)-alkoxy,

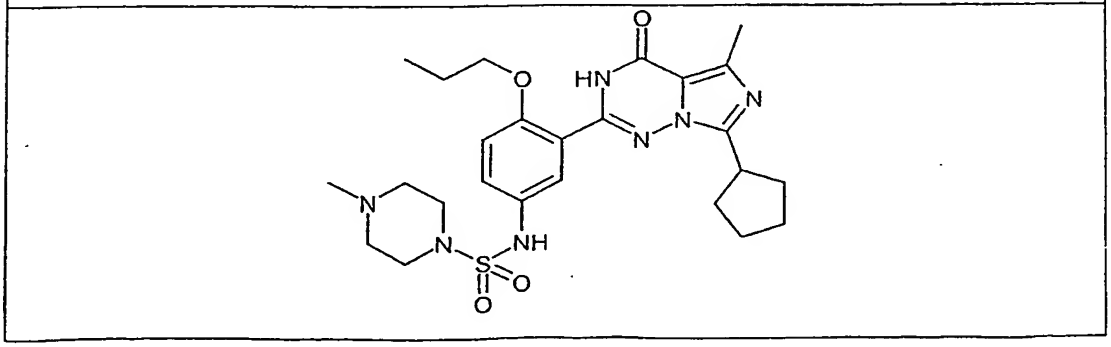
and the N-oxides and/or tautomers thereof, and the pharmaceutically acceptable salts, hydrates and prodrugs thereof.

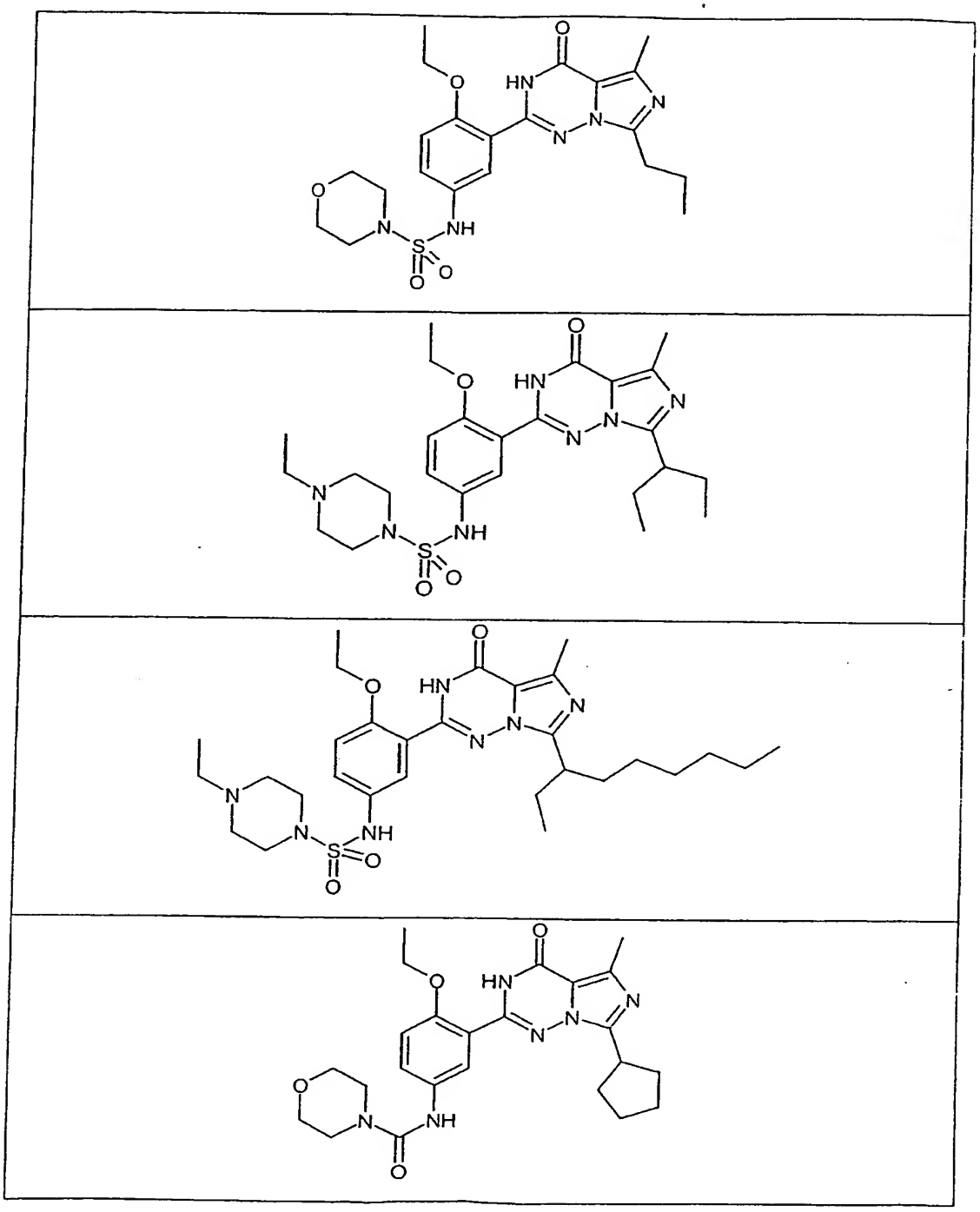
Very particular preference is given to the compounds of the invention having the following structures:

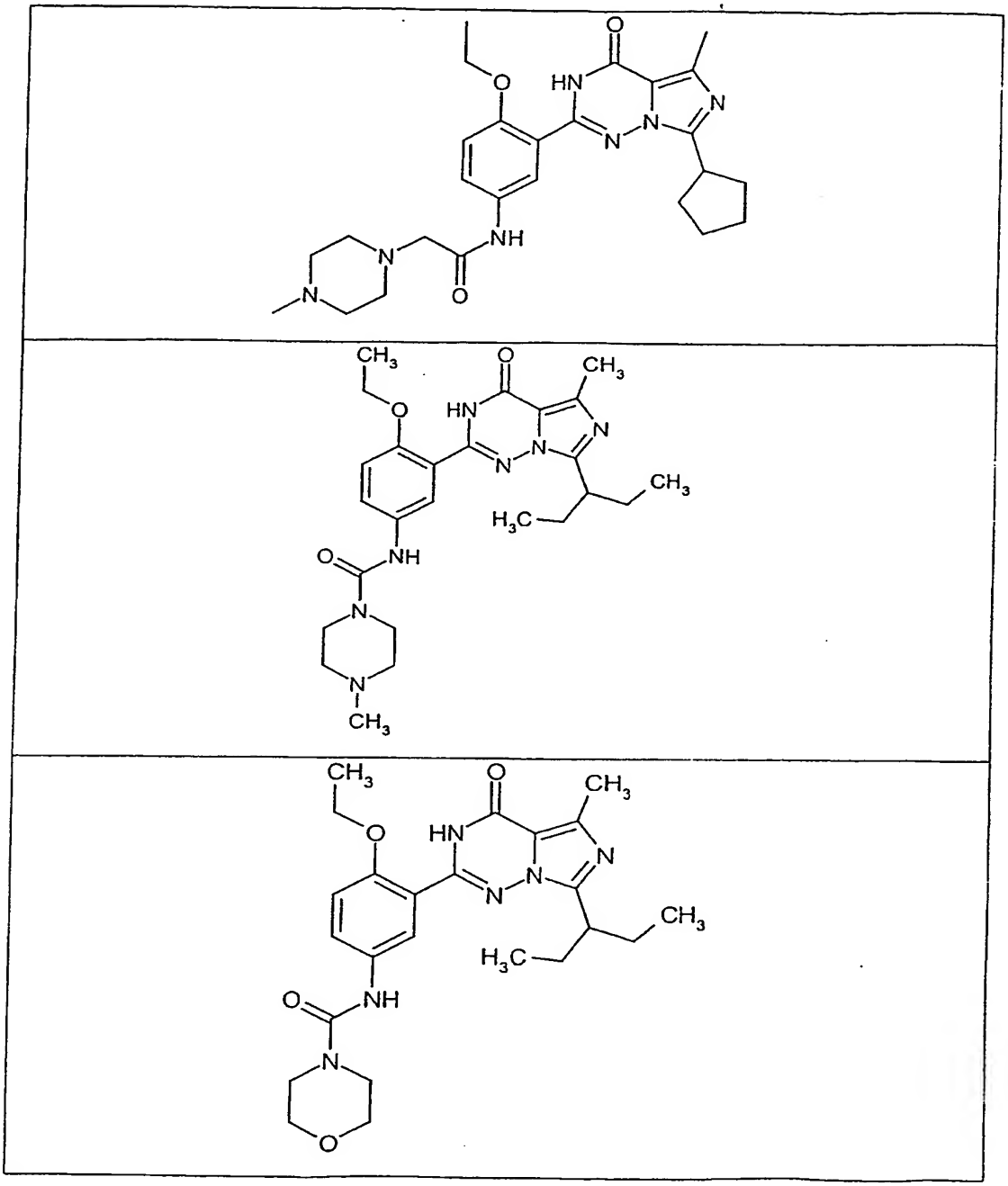


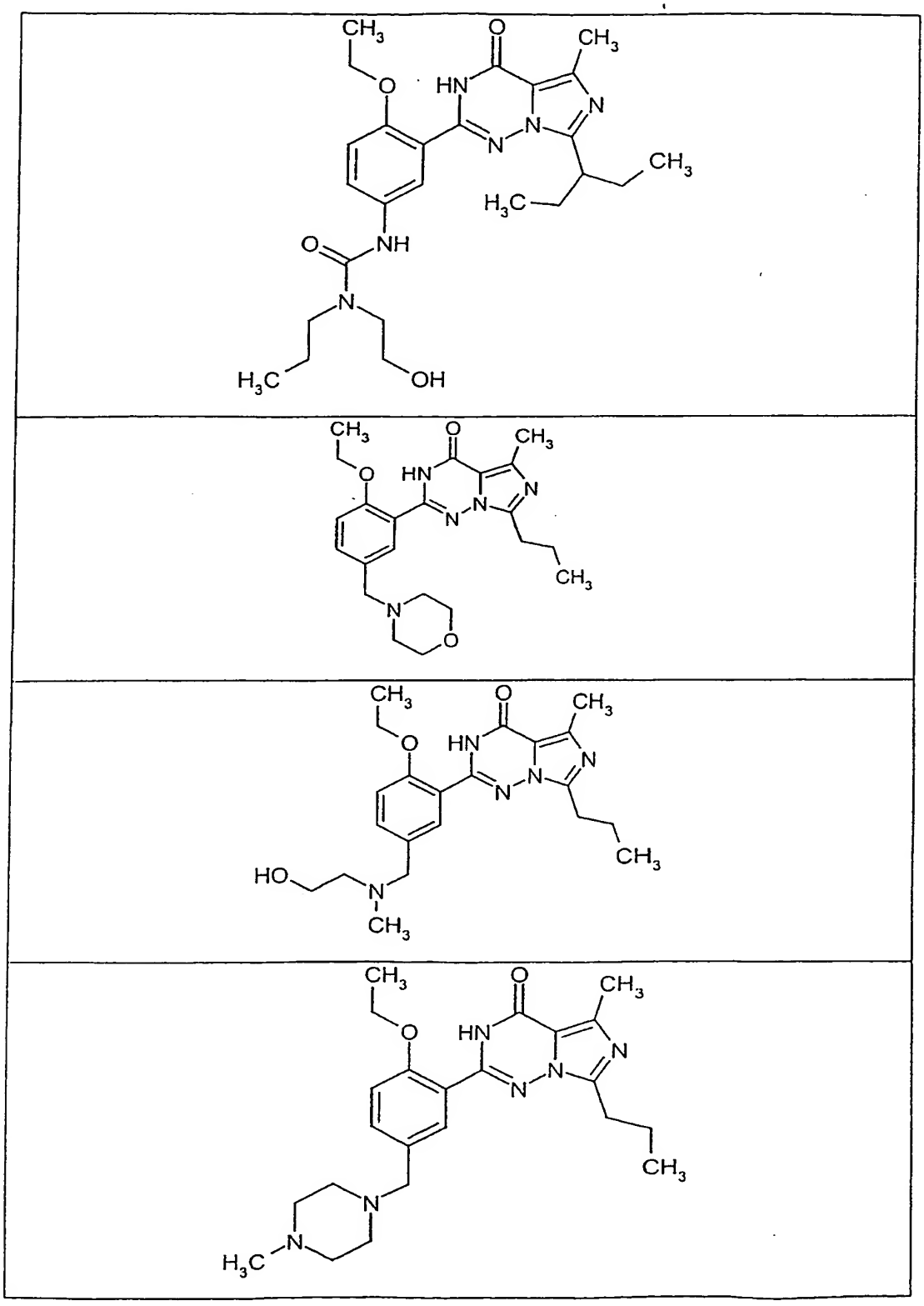


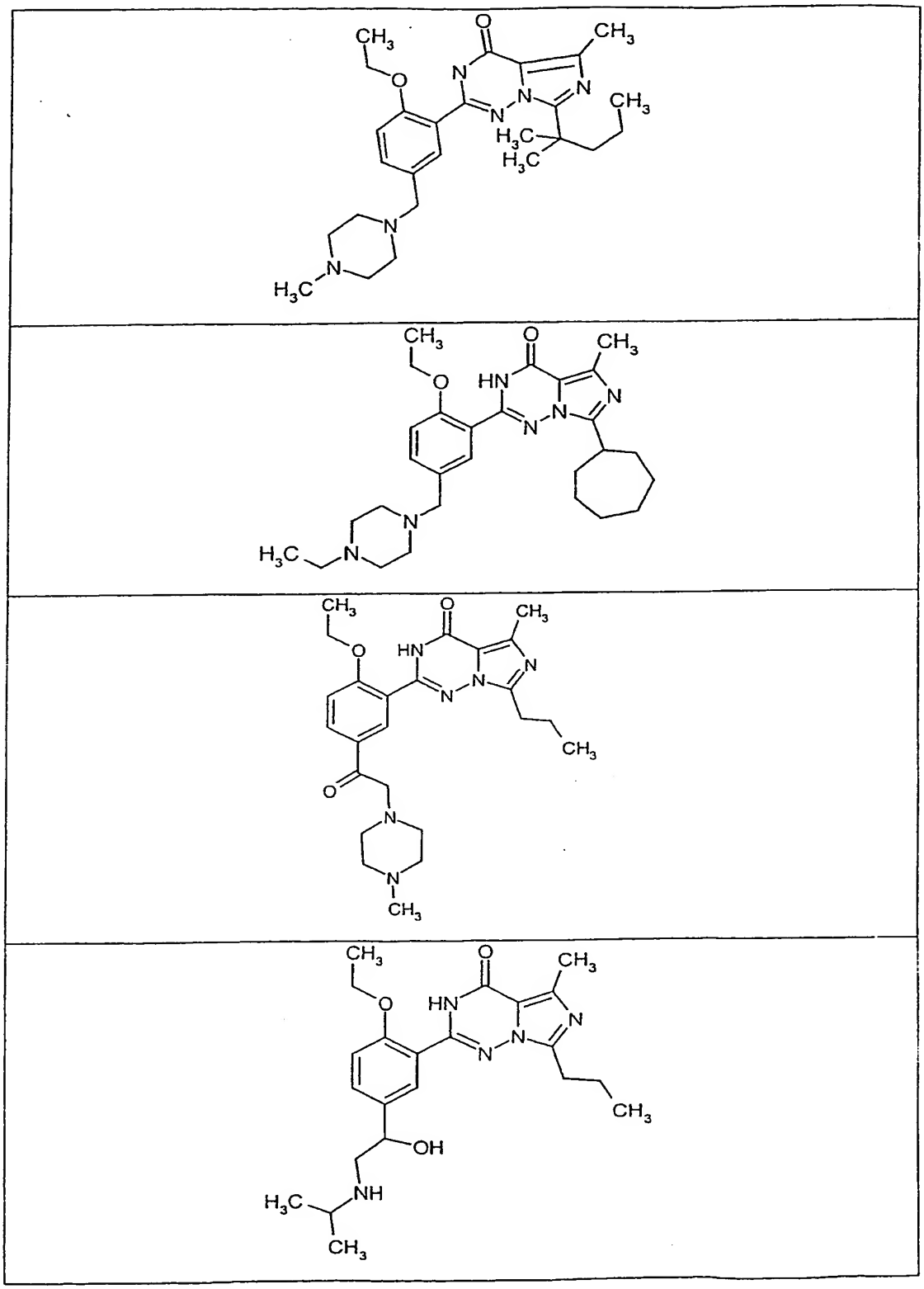


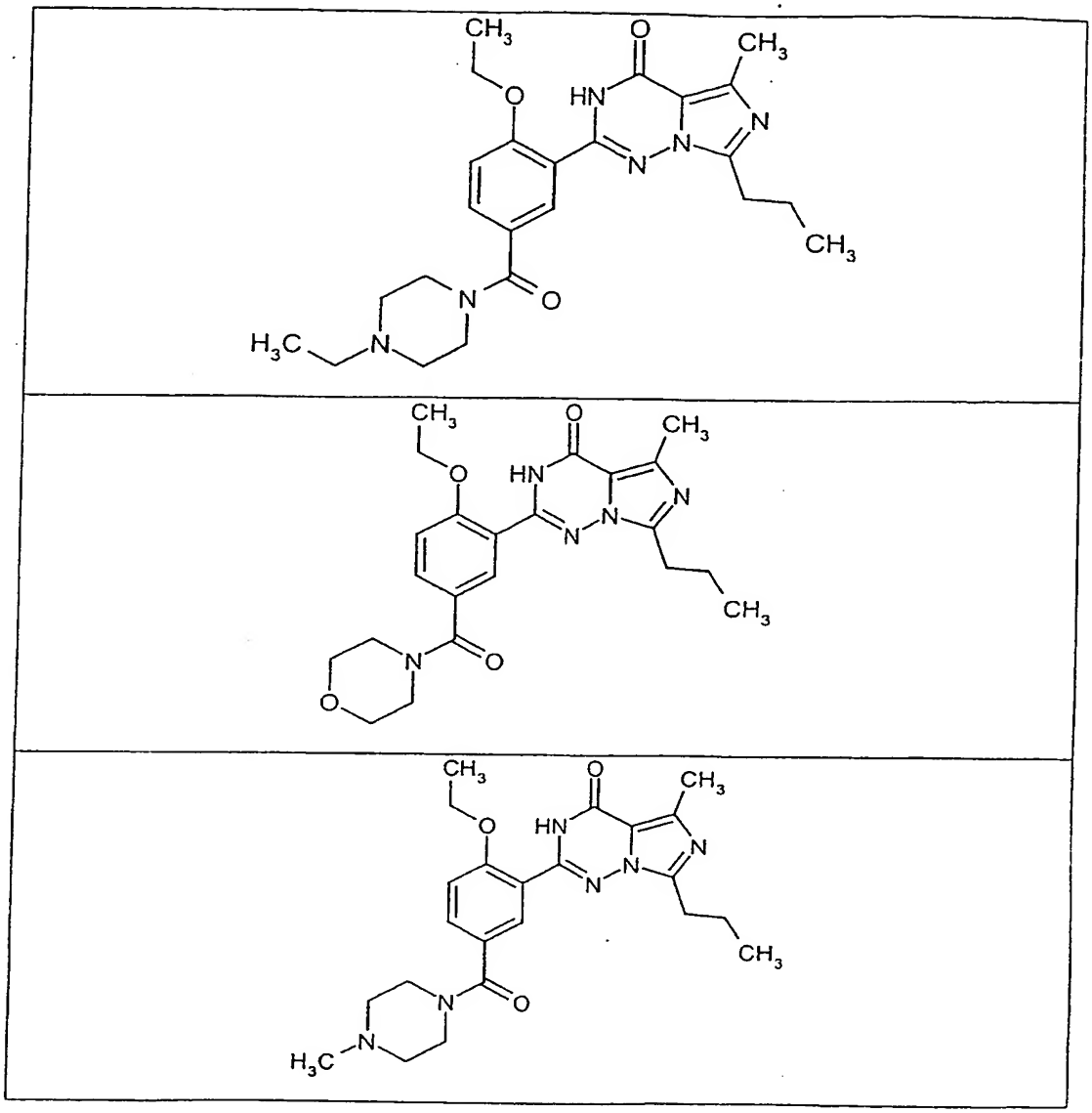












and the tautomers and/or N-oxides thereof, and the pharmaceutically acceptable salts, hydrates and prodrugs thereof.

The compounds used according to the invention and their preparation are described in WO-A 01/64677. Express reference is made to the disclosure of WO-A 01/64677.

The compounds of the general formula (I) which are used according to the invention are suitable for the prophylaxis and/or treatment of disorders in which an increase in

the cGMP concentration is therapeutic, i.e. disorders associated with cGMP-regulated processes (usually referred to simply as 'cGMP-related diseases'). They inhibit either one or a plurality of the cGMP-metabolizing phosphodiesterases (PDE I, PDE II and PDE V). This leads to an increase in cGMP. Differential expression of the phosphodiesterases in different cells, tissues and organs, as well as the differential subcellular localization of these enzymes, make it possible in conjunction with the selective inhibitors of the invention to address selectively the various cGMP-regulated processes.

The relaxant effect on smooth muscle makes them suitable for the treatment of disorders in which an improvement and/or cure of a pathological condition can be achieved by improving the microcirculation of a tissue which comprises a cGMP-metabolizing phosphodiesterase.

The present invention relates to the use of imidazotriazinones for producing a medicament for the treatment and/or prophylaxis of coronary heart disease, heart failure, pulmonary hypertension, bladder disorders, prostate hyperplasia, nitrate-induced tolerance, ocular disorders such as glaucoma, for the treatment or prophylaxis of central retinal or posterior cilliary arterial occlusion, central retinal venous occlusion, optic neuropathy such as anterior ischemic optic neuropathy and glaucomatous optic neuropathy, and of macular degeneration, diabetes, especially of diabetic gastroparesis, for the treatment of disorders of the peristalsis of stomach and esophagus, female infertility, premature labor, preeclampsia, alopecia, psoriasis, the renal syndrome, cystic fibrosis, cancer, for improving perception, for improving concentration, for improving learning and/or memory, especially if the impairment is a consequence of dementia.

In addition, the compounds of the invention enhance the effect of substances such as, for example, EDRF (endothelium derived relaxing factor), ANP (atrial natriuretic peptide), of nitrate vasodilators and all other substances which increase the cGMP concentration in a way different from phosphodiesterase inhibitors.

Activity of phosphordiesterases (PDEs)

The cGMP-stimulable PDE II, the cGMP-inhibitable PDE III and the cAMP-specific PDE IV were isolated either from myocardium of porcine or bovine heart. The Ca^{2+} calmodulin-stimulable PDE I was isolated from porcine aorta, porcine brain or preferably from bovine aorta. The cGMP-specific PDE V was obtained from porcine small intestine, porcine aorta, human blood platelets and preferably from bovine aorta. Purification took place by anion exchange chromatography on MonoQ^R Pharmacia essentially by the method of M. Hoey and Miles D. Houslay, Biochemical Pharmacology, Vol. 40, 193-202 (1990) and C. Lugman et al. Biochemical Pharmacology Vol. 35 1743-1751 (1986).

The enzymic activity is determined in an assay mixture of 100 μl in 20 mM Tris/HCl buffer pH 7.5 which contains 5 mM $MgCl_2$, 0.1 mg/ml bovine serum albumin and either 800 Bq of ^{3}HcAMP or ^{3}HcGMP. The final concentration of the appropriate nucleotides is 10^{-6} mol/l. The reaction is started by adding the enzyme, and the amount of enzyme is such that about 50% of the substrate is converted during the incubation time of 30 min. In order to assay the cGMP-stimulable PDE II, ^{3}HcAMP is used as substrate, and 10^{-6} mol/l unlabeled cGMP is added to the mixture. In order to assay the Ca^{2+}-calmodulin-dependent PDE I, 1 μM $CaCl_2$ and 0.1 μM calmodulin are also added to the reaction mixture. The reaction is stopped by adding 100 μl of acetonitrile containing 1 mM cAMP and 1 mM AMP. 100 μl of the reaction mixture are separated by HPLC, and the cleavage products are determined quantitatively online using a flow scintillation counter. The substance concentration at which the reaction rate is reduced by 50% is measured. Additionally used for assaying was the phosphodiesterase [^{3}H] cAMP-SPA enzyme assay and the phosphodiesterase [^{3}H] cGMP-SPA enzyme assay from Amersham Life Science. The assay was carried out according to the test protocol indicated by the manufacturer. The PDE II activity was determined using the [^{3}H] cAMP SPA assay with addition of 10^{-6} cGMP to the reaction mixture to activate the enzyme. For the PDE I measurement, 10^{-7} M calmodulin and 1 μM $CaCl_2$ were added to the reaction mixture. PDE V was measured using the [^{3}H] cGMP SPA assay.

Object recognition test

The object recognition test is a memory test. It measures the ability of rats (and mice) to distinguish between familiar and unfamiliar objects.

The test was carried out as described: Blokland et al, *NeuroReport* 1998, 9, 4205; Ennaceur et al, *Behav. Brain Res.* 1988, 31, 47-59; Ennaceur et al, *Psychopharmacology* 1992, 109, 321-330; Prickaerts et al, *Eur. J. Pharmacol.* 1997, 337, 125-136.

Inhibition of one or more phosphodiesterases of this type always leads to an increase in the cGMP concentration. The compounds are therefore of interest for all therapies in which an increase in the cGMP concentration can be assumed to be therapeutic.

The investigation of the cardiovascular effects was carried out on normotensive and on SH rats and on dogs. The substances were administered intravenously or orally.

The novel active ingredients and their physiologically acceptable salts (e.g. hydrochlorides, maleates or lactates) can be converted in a known manner into conventional formulations such as tablets, coated tablets, pills, granules, aerosols, syrups, emulsions, suspensions and solutions, using inert, nontoxic, pharmaceutically suitable carriers or solvents. In these, the therapeutically active compounds should be present in each case in a concentration of about 0.5 to 90% by weight of the complete mixture, i.e. in amounts which are sufficient to achieve the stated dosage range.

The formulations are produced for example by extending the active ingredients with solvents and/or carriers, where appropriate with use of emulsifiers and/or dispersants, it being possible, for example when water is used as diluent, where appropriate to use organic solvents as auxiliary solvents.

Administration takes place in a conventional way, preferably orally, transdermally or parenterally, i.e. perlingually, sublingually, conjunctivally, optically, buccally, intravenously, nasally, rectally, by inhalation or as implant.

For use in humans, generally dosages of from 0.001 to 50 mg/kg, preferably 0.01 mg/kg – 20 mg/kg, are administered on oral administration. A dosage appropriate for parenteral administration such as, for example, nasally, buccally or by inhalation via mucous membrane is 0.001 mg/kg – 0.5 mg/kg.

It may nevertheless be necessary where appropriate to deviate from the amounts mentioned, in particular as a function of the body weight or of the nature of the administration route, of the individual response to the medicament, of the nature of its formulation and the time or interval over which administration takes place. Thus, in some cases it may suffice to make do with less than the aforementioned minimum amount, whereas in other cases the stated upper limit must be exceeded. Where larger amounts are administered, it may be advisable to divide these into a plurality of single doses over the day.

The compounds of the invention are also suitable for use in veterinary medicine. For uses in veterinary medicine, the compounds or their nontoxic salts can be administered in a suitable formulation complying with general veterinary practices. The veterinarian is able to establish the mode of use and the dosage according to the species of the animal to be treated.

The present invention is illustrated by the following examples which are, however, not intended to restrict the invention in any way.